Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-123 are pending in this application and are rejected on various grounds. The previous rejections are discussed in view of the change in the assay upon which Applicants rely on for patentable utility, as discussed below.

Continuity

Applicants now rely on assay 94: 'the glucose/FFA uptake assay,' instead of the "gene amplification assay" for patentable utility of PRO1182 and its antibodies (see Example 158, page 530 of the instant specification). This assay was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority to which has been claimed in this application. As discussed below, the glucose/FFA uptake assay was a "well-established assay" around the effective filing date of March 30, 2000. Hence, Applicants believe that they are entitled to an effective filing date of at least **March 30, 2000** for the instant application.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-124 were rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-124 were further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

As discussed above, Applicants now rely on assay 94: 'the glucose/FFA uptake assay,' instead of the "gene amplification assay" for patentable utility of PRO1182 and its antibodies. The adipocyte glucose/FFA uptake assay was designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids by adipocyte cells. The assay identifies polypeptides that are useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is therapeutically effective. Examples of such disorders include, but are not limited to, obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay of the instant application is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1182 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO1182 resulted in less than 0.5 the uptake of the insulin control, PRO1182 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay, as described in Example 158 of the instant application, was a "well-established assay" around the effective filing date of March 30, 2000. Applicants show, by discussing prior publications that were available in the art around the effective filing date of March 30, 2000, that there was an art recognized nexus between proteins that tested positive in the adipocyte glucose/FFA assay and certain disease states. For example, it was well known in the art around March 30, 2000 that, increased glucose uptake by adipocyte cells was the hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al.*, *Endocrinology*, 133(1):352-359 (1993) - copy enclosed with IDS). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds were shown to function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, vanadium salts were considered to be a potential treatment for diabetes, and several clinical trials had already been performed as of the effective filing date of Msrch 30, 2000 (see page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed with IDS). Using the rat adipocyte culture system, similar to the system disclosed in the instant application, Goldwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism

in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. Similar assays were commonly used to identify potential anti-diabetic agents and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism.

Further, Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2): 551-558 (1998) - copy enclosed with IDS). Figure 1A showed the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggested that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and that the increase in leptin was more closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect of two well-known anti-diabetic agents, metformin and vanadium, on leptin secretion. These agents were known to enhance glucose uptake. (Muller *et al., Obesity Research,* 8(7): 530-539 (2000) - copy enclosed with IDS). Mueller's experimental data indicated that both metformin and vanadium increased glucose uptake and inhibited leptin secretion from cultured adipocytes.

The studies discussed above clearly establish that the glucose/FFA uptake assay, as described in the instant application, was a well-established assay useful for identifying therapeutic agents for treating metabolic diseases such as obesity, diabetes, hyper- or hypo-insulinemia, known at the effective filing date of this application. Thus, Applicants respectfully submit that at the effective filing date of the present application, one skilled in the art would have reasonably accepted that molecules activating glucose uptake, like PRO1182, would find real-life utilities in the treatment of metabolic diseases such as diabetes, obesity and related diseases.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1182 and its antibodies. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejections – 35 USC § 112, first paragraph- Deposit rules

Claims 119-123 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the ATCC deposit No. 203088 of the current invention needs the current address of the ATCC and a declaration or statement stating that all restrictions imposed by the depositor on the public be irrevocably removed.

Applicants submit that ATCC deposit No. 203088 was made under the Budapest Treaty, as indicated on page 566 and Applicants further submit that the address of the ATCC is correct as indicated on page 563, line 10 of the instant specification. Applicants have also added the requisite assurances in instant amendments to the specification that irrevocably remove all restrictions imposed by the depositor on the availability of deposited material to the public upon the granting of the pertinent U.S. patent. Accordingly, this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119 and 124 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. The Examiner contends that "neither the specification, nor the art provide unambiguous definitions for "binds" and "specifically binds;" therefore the metes and bounds of the claims cannot be determined by one skilled in the art". Applicants respectfully traverse this rejection.

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants had canceled claim 124 and had amended claim 119 to recite "specifically binds". Applicants submit that the term "specific binding" or "specifically binds" has a well established meaning, and is understood by those skilled in the art to mean that the antibody binds to a particular polypeptide, and does not significantly bind or cross-react with another polypeptide. Accordingly, one skilled in the art would knows what the scope of the invention is. Since claim terms should be given their ordinary, art-recognized meaning, the present rejection is believed to be misplaced, and should be withdrawn.

Accordingly, Applicants respectfully request that this rejection to claims be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C34). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 10, 2005

Daphne Reddy

Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2100910 v1
3/7/05 10:47 AM (39780.2730)